Research Journal of Pharmacognosy (RJP) 9(3), 2022: 85–106
Received: 29 Aug 2021
Final revision: 16 Apr 2022
Accepted: 16 May 2022
Published online: 25 May 2022
DOI: 10.22127/RJP.2021.302028.1781

Review article

Filipendula ulmaria (L.) Maxim. (Meadowsweet): a Review of Traditional Uses, Phytochemistry and Pharmacology

Avishan Farzaneh[1], Abbas Hadjiakhoondi[1,2], Mahnaz Khanavi[1], Azadeh Manayi[2], Roodabeh Bahramsoltani[3], Mahdieh Kalkhorani[1*]

[1]Department of Pharmacognosy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.
[2]Medicinal Plants Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.
[3]Department of Traditional Pharmacy, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran.

Abstract

Filipendula ulmaria (L.) Maxim. commonly known as "meadowsweet", is a perennial herb native to Iran, Europe, and Western Asia. Several medicinal properties of the plant have been reported in Persian medicine. *Filipendula ulmaria* is traditionally used for fever, pain, inflammatory diseases (arthrosis, rheumatism, and arthritis), gastric disorders, liver dysfunction, and gout. The phytochemical studies indicate the presence of several active compounds, mainly phenolic acids, flavonoids, tannins, and terpenoids. Salicylic acid and its derivatives are the most important compounds found in essential oil and extracts of different parts of the plant. Pharmacological evaluations have shown the anti-arthritis, analgesic, anti-inflammatory, anti-oxidant, anti-cancer, anti-coagulant, anti-microbial, immunomodulatory, gastro-protective, and hepato-protective activity of *F. ulmaria*. Despite pharmacological activities, traditional uses and herbal supplements, there is no complete review article on this herb's properties. In this paper, we have provided a review on traditional uses, phytochemicals, pharmacological properties and medical information of this valuable medicinal plant.

Keywords: anti-inflammatory; anti-oxidant; *Filipendula*; meadowsweet; phenolic acid

Citation: Farzaneh A, Hadjiakhoondi A, Khanavi M, Manayi A, Bahramsoltani R, Kalkhorani M. *Filipendula ulmaria* (L.) Maxim. (meadowsweet): a review of traditional uses, phytochemistry and pharmacology. Res J Pharmacogn. 2022; 9(3): 85–106.

Introduction

Filipendula ulmaria (L.) Maxim. belongs to the family Rosaceae, and is native throughout Europe and Western Asia (Near East and the Middle East). The plant is commonly known as meadowsweet and found in abundance in humid areas near water springs [1-2]. Different common names are used in various countries, including mead wort, meadow-wort, the pride of the meadow, queen of the meadow, lady of the meadow, meadowsweet, meadow queen, dollof, and bridewort [3]. Different categories of phytochemicals are found in *F. ulmaria* including phenolic acids, flavonoids, tannins, and terpenoids [4]. Biological and pharmacological effects of *F. ulmaria* such as anti-inflammatory, analgesic, anti-oxidant, anti-microbial, anti-nociceptive, anti-coagulant, anti-arthritic, anti-pyretic, anti-cancer and treating gastric diseases have been described in several studies. In addition, it seems that *F. ulmaria* plays a role in

*Corresponding author: mkalkhorani.pharmacist@gmail.com

treating gout, arthritis, and liver diseases [4–14]. *Filipendula ulmaria* has not been investigated significantly in clinical trials so the reports are mainly derived from traditional uses, in-vitro, and in-vivo studies [15]. Considering the valuable medicinal properties of the plant, this study aims to provide a review on the traditional uses, phytochemistry, and pharmacological properties of *F. ulmaria*.

Methods

Electronic databases including PubMed, Scopus, and Web of Science were searched with the keywords "*Filipendula ulmari*a" and "meadowsweet" to collect all published articles until 2020. All articles with these two words were reviewed. The number of 331 related articles from the Scopus database, 183 articles from Pubmed, and 246 articles from Web of Science were checked. Similar articles were excluded and 363 articles were screened based on the full text, which eventually led to several studies cited in the reference section for the topics we considered in this article. All types of articles and studies including phytochemistry and pharmacology properties of the plant were examined. In addition to the articles mentioned, the traditional use of the plant as well as the description of the plant in some pharmacopeias were investigated. The products and applications of *F. ulmaria* which were described in Martindale reference were also mentioned in our review article.

Results and Discussion

Botany and ethnomedicinal uses

Filipendula ulmaria is a perennial, herbaceous, erect plant; the stems are 50 to 200 cm long with reddish to purple color. The flowering season is from summer to early autumn when clusters of creamy-white graceful flowers blossom. The flowers have small and numerous petals with strong pleasant scent. The leaves are divided and made up of two or more discrete leaflets, with large serrate pinna and small intermediate ones [16,17]. Since the plant has a favorable taste and smell, the whole plant parts are used in aromatic products and food industries [18]. Traditionally, the infusion, liquid extract, tincture and decoction of meadowsweet flower reported to have anti-rheumatic, analgesic, anti-pyretic and anti-inflammatory properties [14]. The medicinal application of *F. ulmaria* has been mentioned since the late 16^{th} and 17^{th} centuries. Traditionally, this herb was used as a diuretic and a remedy for inflammatory diseases [20–23]. For instance, in the traditional medicine of Australia, tea of flowers or leaves has been used to treat infections, rheumatism, fever, and gout. Other beneficial effects of the plant such as anti-rheumatic, anti-acid, mild urinary anti-septic properties, healing effect in gastritis, dyspepsia, and peptic ulcer are also mentioned [23,24]. In Europe, the plant is traditionally used in cases of diarrhea, eye disturbances, feeling nervous, snake bite, cough, erysipelas, and rabies. It has also been traditionally applied as anti-pyretic, analgesic and topically for treating the symptomatic painful articular conditions (Table 1) [13,23].

Phytochemistry

Flavonoids, tannins, phenolic acids, terpenoids, and other secondary metabolites have been extracted from the plant using different solvents such as water, ethanol, and methanol. Table 2 represents the phytochemical constituents isolated from different parts of *F. ulmaria*.

Phenolic compounds

Phenolic compounds, including phenolic acids, flavonoids, tannins, and lignans, are a large group of phytochemical compounds found in *F. ulmaria*. They imply important properties, including anti-cancer, anti-oxidant, anti-microbial, and anti-inflammatory effects [34-40]. There is a little phytochemical information on the phytochemicals found in other *Filipendula* species. [41,42].

Phenolic acids

Meadowsweet contains large groups of phenolic acids, most commonly found in the aerial parts. Cinnamic acid, caffeic acid and its derivatives, ferulic acid, veratric acid, coumaric acid, vanillic acid, and syringic acid are famous with potential therapeutic activities (Figure 1 and Table 2) [43].Ten phenolic acids were isolated and reported in 2013 from the flowers and leaves of *F. ulmaria* by HPLC method [44]. The aerial parts, flowers, and leaves of *F. ulmaria* contain salicylic acid, methyl salicylate, salicin, and salicyl alcohol [45,46]. In 2010, Blazics et al. identified six salicylates from the methanol extract of *F. ulmaria* by LC-DAD-MS–MS triple quadrupole system.

Table 1. Information on traditional indications and preparations of *Filipendula ulmaria* in European countries

Part used	Mode of preparation	Indication	Reference
Herb, Flower	Infusion, tincture, decoctions, alcoholic extracts	Diaphoresis, flu, colds, chills	[19-21,25,30-32]
Herb, Flower	Infusion, liquid extract (1:1 in 25% alcohol), tincture (1:5 in 45% alcohol	Rheumatic diseases, arthritis	[20-23,25-28,33]
Herb, Flower	Infusion, liquid extract, tinctures	Renal diseases	[20- 22, 32]
Herb, Flower	Infusion, liquid extract (1:1 in 25% alcohol), tincture (1:5 in 45% alcohol)	Gastritis, peptic ulcer, acute cystitis, diarrhea in children	[20,22,23,26,29]
Herb	Infusion, tincture	Muscle spasms, bile tract diseases	[21]
Herb, Flower	Infusion, tincture, liquid extract	Cystitis, pyelitis, nephritis, scarlet fever wound, cellulitis	[21,22,33]

Salicylic acid and its derivatives are the most important compounds found in essential oil and extracts of different parts of the plant, which have shown analgesic, anti-inflammatory, and anti-coagulant effects [47]. Salicylates are also used as anti-pyretic, anti-rheumatic, and analgesic [13,48].

Flavonoids

Flavonoids are a widespread group of polyphenolic compounds with several biological activities [49–51]. In both exudative and proliferative phases of inflammation, flavonoids have potential effects on reducing inflammation and beneficial effects on inhibition of enzymes such as xanthine oxidase, Ca^{+2}-ATPase, aldose reductase, lipoxygenase, phosphodiesterase, and cyclooxygenase [52-56]

Several flavonoids have been isolated and identified from the aerial parts of *F. ulmaria* (Table 2). Anti-angiogenic and anti-metastatic activity of *F. ulmaria* could be attributed to kaempferol, luteolin and quercetin [49]. In addition, apigenin and quercetin have shown antimicrobial, anti-helicobacter, and anti-inflammatory effects in some studies [50]. Based on reports, the most abundant flavonoids identified in *F. ulmaria* were quercetin, spiraeoside, isoquercitrin, rutin, kaempferol, and hyperoside (Table 2, Figure 2).

Tannins

Ellagic acid, ellagitannins such as tellimagrandin (I, II), rugosin (A, B, E, D), pedunculagin, and casuarinin were isolated in particular from polar extracts of *F. ulmaria* aerial parts. Catechins, epicatechin and procyanidin were also elucidated from *F. ulmaria* (Figure 3) [65].

Terpenoids

Among the phytochemicals, terpenoids (isoprenoids) show a high diversity of secondary metabolites, widely produced by many plants and some insects [58,59]. A total of four triterpenoids (tormentoside, ursolic acid, promolic acid, medicoside J) and one isoprenoid (β-carotene) have been isolated from the aerial parts of *F. ulmaria* using alcoholic extracts. Several studies suggest that triterpenes possess several bioactivities. For example, ursolic acid has inhibitory effects against four tumor cell lines (Bel-7402, BGC, HL-60, and Hela) [57].]. In addition, pomolic acid was the most cytotoxic component and was specific for M-14 melanoma and ME180 cervical comparable to ursolic acid, 3-O-acetylpomolic acid, 2-oxopomolic acid , with GI_{50} values of 6.9 and 8.3 μg/mL respectively [59]. In isoprenoids group, beta-carotene is the most common form of carotene in plants (such as meadowsweet), which is a precursor of vitamin A in the body [60].

Miscellaneous compounds

Except for the compounds mentioned in the phytochemical section, some chemicals such as carbohydrates and amino acids have also isolated from *F. ulmaria* (Table 2).

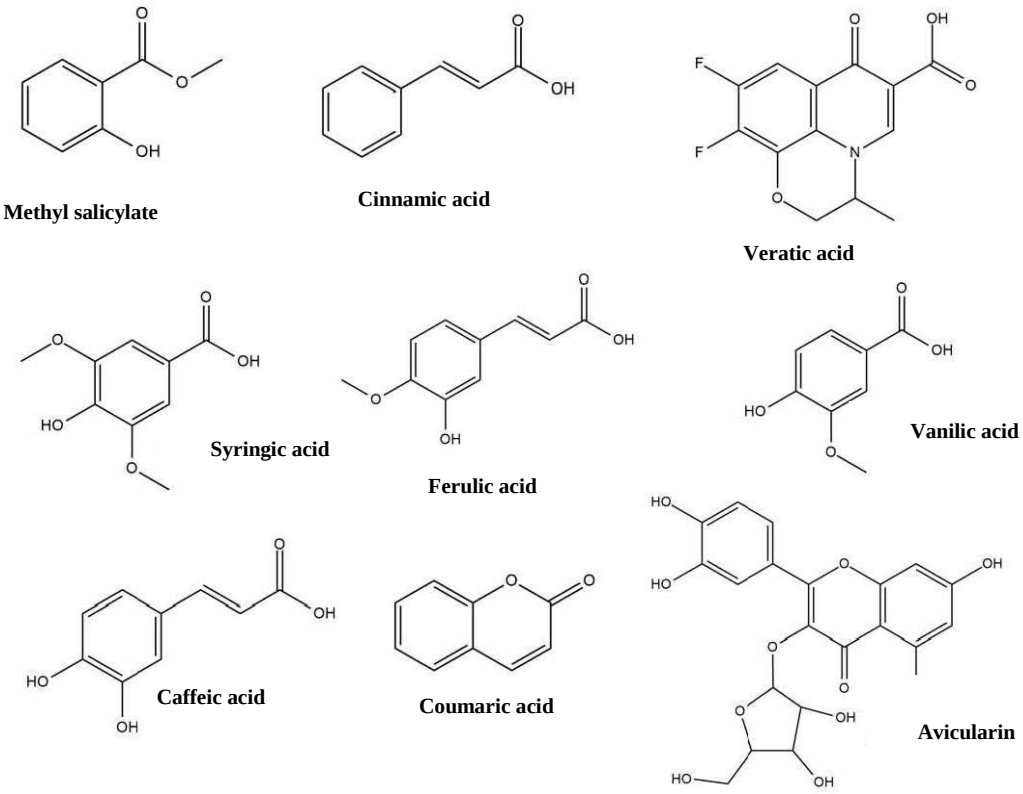

Figure 1. Structures of some of the isolated phenolic acids from *Filipendula ulmaria*

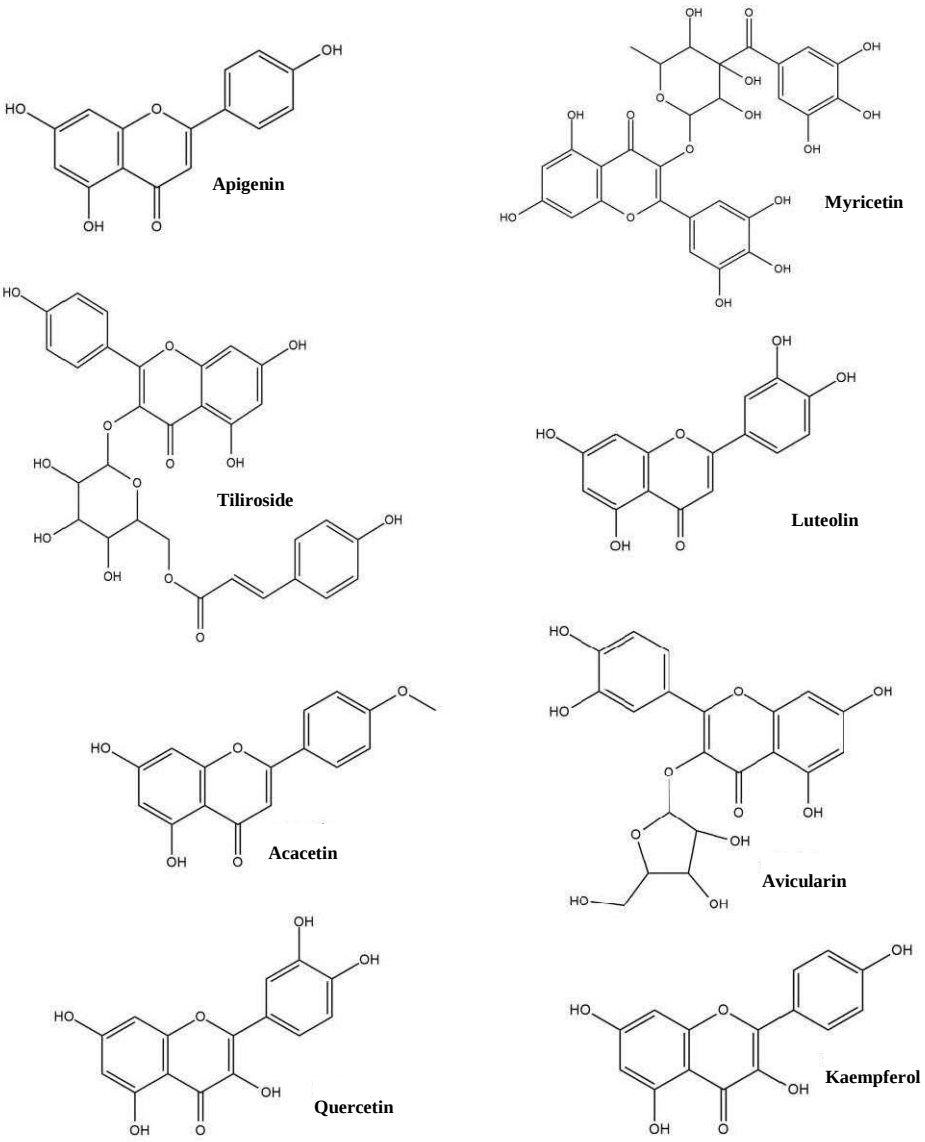

Figure 2. Structures of some flavonoids from *Filipendula ulmaria*

Table 2. Phytochemicals identified in *Filipendula ulmaria*

Phytochemical category	Phytochemical name	Part	Solvent of extraction*	Reference
Amino acid	Histidine methyl ester	Flowers	EtAc	[61]
Benzoic acid	*m*-Hydroxybenzoic	Flowers	Et_2O	[62]
	p-Hydroxybenzoic acid	Flowers, leaves	EtOH	[44]
	2,3-Dihydroxybenzoic	Flowers	Et_2O	[62]
	o-Anisic acid	Flowers	EtOH	[44]
	Methyl-o-anisate	Flowers	EtOH	[44]
	Vanillic acid	Leaves	Et_2O	[63]
	3,4-Dihydroxy-benzoic acid	Aerial parts	Acetone80%	[64]
Carbohydrate	Sucrose	Aerial parts	MeOH	[65]
	Trehalose	Aerial parts	MeOH	[65]
Carboxylic acid	2-Pyrone-4,6- dicarboxylic acid	Aerial parts	MeOH	[65]
Flavonoid	Quercetin	Flowers, leaves, aerial parts	Et_2O, Aq, MeOH 50%, MeOH 80%, MeOH, EtOH, Aq and EtOH	[10,44,57,62-73]
	Quercetin-3-O-β-D-glucoside	Flowers	Aq– MeOH 80%	[61,69]

Table 2. Continued

Phytochemical category	Phytochemical name	Part	Solvent of extraction*	Reference
	Quercetin3-O-glucuronide (Miquelianin)	Leaves Aerial parts	EtOH - MeOH	[44,65]
	Quercetin-3-O-α-L-arabinoside	Flowers	Aq	[69]
	Quercetin-4'-O-β-D-glucoside (Spiraeoside - Spiraein)	Flower, Leaves, aerial parts	Aq- Aq. MeOH50% - EtOH MeOH80% - MeOH– Aq. EtOH	[6,10,44,47,61,67-74]
	Quercetin-3-O-α-L-rhamnoside	Flowers	Aq	[69]
	Quercetin-3-O-b-rhamnoside	Leaves	Aq	[71]
	Quercetin-3-O-β-D-glucuronide	Flowers, leaves	Aq	[69,71]
	Quercetin *O*-pentoside	Aerial parts	MeOH 80%	[61]
	Quercetin-4′-O-β-galactopyranoside (filimarin)	Aerial part	EtOH (70%)	[66,75]
	Quercetin-3-O-β-glucopyranoside (Isoquercitrin)	Aerial part-flowers, leaves	Aq. MeOH50%, MeOH, EtOH	[44,65-67,70]
	Quercetin3-O-β-(2″-O-galloyl)-D-galactopyranoside	Flowers	Aq	[12]
	Quercetin3-O-β-(2″-O-galloyl)-D-glucopyranoside	Flowers, aerial parts	Aq - MeOH	[6,12]
	Quercetin-3-O-b-rutinoside (rutin)	Flowers, leaves, Aerial parts	Aq. MeOH50%, Aq, MeOH, MeOH80%, EtOH, Aq.EtOH	[10,44,61,65,68,70-73, 76,77]
	Quercetin-3-O-galactoside	Flowers	EtOH, Aq.EtOH	[68]
	Quercetin –o - dihexoside	Aerial parts	MeOH	[65]
	Apigenin	Flowers	Et_2O	[62]
	Kaempferol	Flowers, leaves Aerial parts	Et_2O - Aq. MeOH50%- Aq-EtOH –Aq.EtOH	[10,62,67,68,70,71]
	Kaempferol 7-*O*rutinoside	Flowers, leaves	Aq. MeOH50%	[44,70]
	Kaempferol-3-O-α-L-rhamnoside	Flowers	Aq	[69]
	Kaempferol-3-O-glucoside (astragalin)	Leaves, aerial parts, flowers	MeOH- EtOH –Aq.EtOH	[65,67,68]
	Kaempferol-4'-O-β-D-glucoside	Flowers, leaves, aerial parts	Aq– MeOH80%	[69,71,73,78]
	Kaempferol-4-O- glucoside	Leaves	EtOH	[44]
	Kaempferol 3-O-β-(2″-O-galloyl)-D-glucopyranoside	Flowers	Aq	[12]
	Kaempferol-3-O-b-rutinoside (nicotiflorin)	Leaves	Aq	[71]
	Kaempferol –o-hexoside - deoxyhexoside	Aerial parts	MeOH	[75]
	Hyperoside (quercetin-3-galactoside	Flowers, leaves, aerial parts	Et_2O - Aq. MeOH50%– MeOH - EtOH	[6,72,65,67,70,72,73]
	Myricetin	Flowers	Et_2O - Aq. MeOH50%	[62,63,70]
	Myricetin3-O-β-glucuronide	Flowers	Aq. MeOH50%	[70]
	Luteolin	Flowers	Et_2O - EtOH – Aq.EtOH	[62,67]
	Luteolin-7-O-glucoside	Aerial parts	MeOH	[6,72]
	Protocatechuic acid	Flowers	Et_2O - Aq - Aq. MeOH50%	[62,69,70]
	Tiliroside	Flowers	Aq. MeOH50%	[70]
	Procyanidins B1	Leaves	EtOH	[44]
	Procyanidins B2	Leaves, aerial parts	EtOH- MeOH	[44,65]
	Procyanidin C1	Aerial parts	EtOH 80%	[78]
	Isorhamnetin *O*-hexoside	Flowers, aerial parts	EtAc - MeOH	[61,65]
	Isorhamnetin acetylhexoside	Flowers	EtAc	[61]
	Avicularin/Avicularoside	Aerial parts	MeOH- MeOH80%- EtOH	[65,67,73]
	Acacetin	Aerial parts	MeOH 80%	[73]
Phenolic acid	Salicylic acid monohexoside	Herb, flowers	MeOH	[48]
	Salicylic acid hexoside	Aerial parts	MeOH	[65]
	Isosalicin	Aerial parts	MeOH	[65]
	Salicin	Herb, flowers, leaves	MeOH - Aq-EtOH70%	[48,79]

Table 2. Continued

Phytochemical category	Phytochemical name	Part	Solvent of extraction*	Reference
	Salicylalcohol	Herb, flowers	MeOH	[48]
	Methyl salicylate	Flowers, leaves	Aq- EtOH	[44,69]
	Menotropin (Methyl salicylate-GX)	Herb, flowers, aerial parts	MeOH	[47,48,65]
	Spiracin	Aerial parts	MeOH	[65]
	3,5-Dihydroxybenzoic acid (α-resorcylic acid)	Flowers	Et_2O	[62]
	p-Coumaric acid	Flowers, aerial parts	Et_2O - MeOH	[62,65]
	o-Coumaric acid	Flowers	Et_2O	[62]
	Aesculetin	Aerial parts	MeOH	[65]
	Veratric acid	Flowers	Et_2O	[62]
	Caffeic acid	Flowers, leaves	Et_2O – Aq - MeOH80% - Acetone 80%	[44,62-64,69]
	1,3-Di-O-caffeoylquinic acid	Flowers, leaves, aerial parts	Aq -MeOH	[5,44,65]
	4-*O*- caffeylquinic acids	Leaves	EtOH	[44]
	3-*O*- caffeoylquinic acids	Leaves	EtOH	[44]
	3,4-di-*O*-caffeoylquinic acids	Leaves	EtOH	[44]
	Caffeoyl threonic acid	Aerial parts	MeOH	[6]
	Syringic acid	Flowers – Aerial parts	EtOH – MeOH – Aq.EtOH	[44,65,68]
	p-Coumaric acid	Flowers- leaves	EtOH	[44,63]
	Ferulic acid	Flowers-leaves	Et_2O	[62,63]
	Vanillic acid	Flowers-leaves	Et_2O	[62,63]
	Cinnamic acid	Flowers, leaves	EtOH	[44]
	3,4 Dihydroxy cinnamic acid	Aerial parts	MeOH	[65]
	Chlorogenic acid	Aerial parts, flowers	MeOH – Acetone 80% - EtOH – Aq.EtOH	[6,64,65,68,72,80]
Tannin	Ellagic acid	Flowers, leaves, aerial parts- root	Et_2O – Aq- Aq. MeOH50% - MeOH – EtOH – Aq.EtOH	[6,10,44,62,65,67–70]
	Gallic acid	Flowers, leaves, aerial parts, root	Et_2O – Aq - Aq. MeOH50%- MeOH - MeOH80% - Acetone 80% - EtOH – Aq.EtOH	[6,62-65,68,70,72]
	Tellimagrandin I	Aerial parts, flower	MeOH- Aq - Aq. MeOH50%	[65,57,58]
	Tellimagrandin II	Flowers, leaves, aerial parts	Aq – Aq. MeOH50% -EtAc - MeOH	[44,61,65,69,70)
	Rugosin A	Flowers, aerial parts	Aq. MeOH50% -EtOAc - MeOH	[61,65,70]
	Rugosin A methyl ester	Flowers	EtAc	[61]
	Rugosin B	Flowers, aerial parts	Aq. MeOH50%- MeOH	[65,70]
	Rugosin B1	Flowers	Aq	[69]
	Rugosin B2	Flowers	Aq	[69]
	Rugosin E	Flowers, aerial parts	Aq. MeOH 50%- MeOH	[65,70]
	Rugosin E1	Flowers, leaves	Aq	[44,69]
	Rugosin E2	Flowers, leaves	Aq	[44,69]
	Rugosin D	Flowers, leaves, aerial parts	Aq - Aq. MeOH50%- EtAc- MeOH	[44,61,65,69,70]
	Pedunculagin	Aerial parts	MeOH	[65]
	Casuarinin/ Casuaricin	Aerial parts	MeOH	[65]
	Epicatechin	Flowers, leaves, aerial parts, root	Aq.MeOH 50% - MeOH- EtOH- Aq.EtOH- EtOH 80%	[10,44,65,68,70,78]
	Catechin	Flowers, aerial parts, root	Aq. MeOH50% – MeOH – EtOH – EtOH80%	[6,10,44,63,65,70,72,78]
	Epigallocatechin	Leaves, aerial parts, flowers	EtOH- Aq.EtOH- MeOH-	[44,65,68]

Table 2. Continued

Phytochemical category	Phytochemical name	Part	Solvent of extraction*	Reference
	Epicatechingallate	Leaves	EtOH	[44]
	Epigallocatechingallate	Leaves	EtOH	[44]
	3-*O*-galloylquinic acids	Leaves	EtOH	[44]
	5-*O*-galloylquinic acids	Leaves	EtOH	[44]
	Digalloyl-hexahydroxydiphenoyl glucoses	Aerial parts , flowers	MeOH -EtAc	[61,72]
	Digalloyl-hexahydroxydiphenoyl -hexose	Aerial parts	MeOH	[6]
	Dimer of trigalloyl-hexahydroxydiphenoyl hexose	Aerial parts	MeOH	[6]
	Digalloyl coumaroylthreonic acid	Aerial parts	MeOH	[6]
	Trigalloyl-hexahydroxydiphenoyl -hexose	Aerial parts	MeOH	[6]
	Trigalloyl hexahydroxydiphenol glucose	Flowers	EtAc	[61]
Terpenoid (Triterpenoid)	Tormento side	Aerial parts	MeOH	[65]
	Ursolic acid	Aerial parts	MeOH	[65]
	Pomolic acid	Aerial parts	MeOH	[65]
	β-Carotene	Aerial parts	MeOH	[65]
	Medicoside J	Aerial parts	EtOH 80%	[75]

*Aq: aqueous; MeOH: methanol; EtOH: ethanol; EtAc: ethyl acetate

Essential oil

The essential oil of *F. ulmaria* aerial parts mainly contain simple phenols, monoterpenes, sesquiterpenes, saturated and unsaturated aliphatic hydrocarbons and ketones [18,47,69,81]. Taking together, 96 compounds have been found in the essential oil of the plant. Salicylic aldehyde (35.7%- 38.2%), methyl salicylate (18.4%-20.22%), ethyl salicylate (0.19% –1.1%) and benzyl silicate (6.3%) are the major identified compounds; α-Terpineol (1.3%-2.2%), β-ionone (1.3%-1.8%), nonanal (4.75%), linalool (2.03%–2.7%), lilac aldehyde (1.59%), germacrene (1.2%), benzyl alcohol (0.25%– 1.4%), β-caryophyllene (1.6%), pelareonic acid (1.14%), 2-heotadecanone (6.65%), pentacosane (3.50%), decanal (0.07%), pentadecanal (1.9%), hexadecanal (5.2%), heptadecanal (6.9%), trans-anethol (2.2%), C-3-hexenyl acetate (5.53%), C-3-hexanol (1.23%), and cadalene (6.18%) are also isolated from essential oil of *F. ulmaria*. Other compounds that have values of less than 1% are shown in Table 3. One of the most important components is β-damascenone, which is almost 10 times comparable to rose oil. β-Damascenone presence in rose perfume might contribute remarkably to the sensory properties of *F. ulmaria* essential oil [18].

Pharmacological activity

Anti-arthritis, analgesic activity

In a randomized, double-blind study on 20 adults, (average age 67 years with knee osteoarthritis) were exposed to several diets and medications for 10 weeks, as a result, the group using the herbal medication (11 formulated herb) experienced significant improvement over the placebo group. One of the herbs used in this study was *F. ulmaria*, which has been described in numerous references for anti-nociceptive and anti-inflammatory effects [83]. *Filipendula ulmaria* can inhibit COX and consequently, the production of pro-inflammatory mediators (PGs) due to presence of salicylic acid or its CH_3 – or –$COCH_3$ derivative. Thus, *F. ulmaria* can be used as a strong analgesic in arthritis, joint and rheumatic pain [9,84,85].

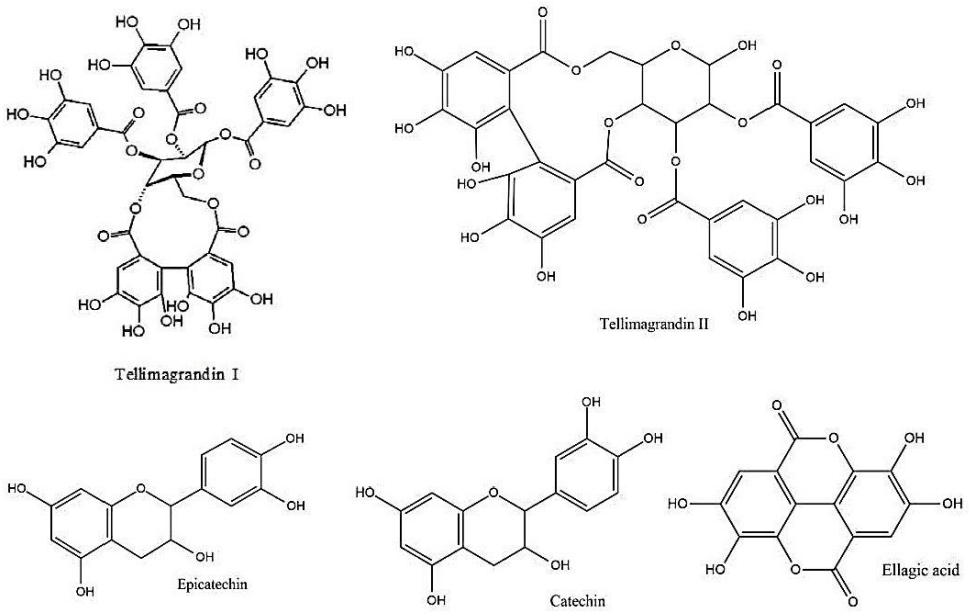

Figure 3. Structures of some tannins from *Filipendula ulmaria*

Table 3. Identified components of *Filipendula ulmaria* essential oil

NO.	Compound	%	Ref.
1	Salicylic aldehyde	38.20 – 36.00- 35.70	[18,47,69,81]
2	Methyl salicylate	20.22 – 19.00 – 18.40	[18,47,69,81]
3	Ethyl salicylate	0.19 – 1.10	[18,69]
4	Benzyl salicylate	6.30	[69]
5	Decane	0.05	[18]
6	o-Pinene	0.10	[18]
7	α-Terpineol	1.30 – 2.20	[69,81]
8	β-Ionone	1.30 - 1.80	[69,81]
9	δ-Amorphene	0.4	[69]
10	Hexanal	0.04	[18,81]
11	2-Hexenal	trace	[81,82]
12	Heptanal	0.15	[18]
13	β-Pinene	0.02	[18]
14	Dodecane	0.02	[18]
15	Limonene	0.07-0.70	[18,81]
16	T-B-Ocimene	0.02	[18]
17	T-Teroinen	trace	[18]
18	Octanal	0.11	[18]
19	C-3-Hexenyl acetate	5.53	[18]
20	C-3-Hexanol	1.23	[18]
21	Nonanal	4.75	[18,81]
22	Pentadecane	0.06	[18]
23	Decanal	0.07	[18]
24	Benzaldehyde	5.42-0.13- 2.3	[18, 69,81,82]
25	Linalool	2.03 – 2.7 – 2.3	[18,69,81]
26	Lilac aldehyde (4 isomers)	1.59	[18]
27	Undecanal	0.32	[18]
28	Lavandulol	0.03	[18]
29	Lilac alcohol (2 isomers)	0.13	[18]
30	Tridecanal	0.22	[18]
31	β -Damascenone	0.76	[18]
32	Geraniol	0.53 – 1.4- 0.3	[18,69,81]
33	Geranyl acetone	0.16	[18]
34	Germacrene	1.20	[69]
35	Benzyl alcohol	0.25 – 1.40	[18,69]

Table 3. Continued

NO.	Compound	%	Ref.
36	Nonadecane	0.36	[18]
37	β-Phenylethyl alcohol	0.39	[18]
38	Anisaldehyde	0.39	[18]
39	p-Anisaldehyde	trace	[82]
40	Caprylic acid	0.88	[18]
41	Caryophyllene oxide	trace	[69]
42	β-Caryophyllene	1.60	[69]
43	Hexyl benzoate	0.27	[18]
44	Heneicosane	0.36	[18]
45	Hexahydro-Farnesyl acetone	0.09	[18]
46	C-3-Hexenyl benzoate	0.05	[18]
47	Pelargonic acid	1.14	[18]
48	Eugenol	0.06	[18]
49	Docosane	0.10	[18]
50	2-Heptadecanone	6.65	[18]
51	Capric acid	0.05	[18]
52	Tricosene	3.67	[18]
53	Tricosene	0.05	[18]
54	2-Octadecanone	0.06	[18]
55	Octadecanal	0.10	[18]
56	Undecanoic acid	0.30	[18]
57	Tetracosane	0.31	[18]
58	2-Nonadecanone	0.60	[18]
59	Pentacosane	3.50	[18]
60	Pentacosene	0.06	[18]
61	Eicosanal	0.28	[18]
62	Benzyl benzoate	0.08	[18]
63	Ethyl benzoate	trace – 0.99-0.30	[15,69]
64	Heptacosane	0.56	[18]
65	Myristic acid	0.01	[18]
66	Vanillin	0.90	[69]
67	Humulene	0.90	[69]
68	*E*-asarone	0.60	[69]
69	Decanal	1.60	[69]
70	Dodecanal	0.30	[69]
71	Tetradecanal	0.40	[69]
72	Pentadecanal	1.90	[69]
73	Hexadecanal	5.20	[69]
74	Heptadecanal	6.90	[69]
75	*n*-Docosane	0.30	[69]
76	*n*-Tricosane	0.20	[69]
77	*n*-Tetracosane	0.70	[69]
78	*n*-Pentacosane	0.30	[69]
79	Thymol	trace	[81]
80	Carvacrol	trace	[81]
81	Guaiazulene	trace	[81]
82	Dibutyl phthalate	trace	[81]
83	2-Amylfuran	trace	[81]
84	Menthol	trace	[81]
85	Menthol	trace	[81]
86	T-Anethole	2.2	[81]
87	Carvone	trace	[81]
88	Piperitone	trace	[81]
89	Isoamyl alcohol	0.34	[18]
90	ρ-Cymene	1.30	[18]
91	Camphor	1.4	[18]
92	Benzonitrile	0.85	[18]
93	Methvl benzoate	34.23	[18]
94	Anisaldehvde	1.82	[81,18]
95	Methyl palmitate	0.15	[18]
96	Cadalene	6.18	[18]

Anticoagulant activity

Meadowsweet flower has been reported to contain heparin-like compounds such as salicylates and its derivatives bound to plant proteins; the *in-vitro* and *in-vivo* studies showed that the plant shows anticoagulant activity [86]. All parts of the plant, in particular the extract of seeds have shown high anticoagulant effects in different studies [87]. In vivo studies also presented that injections of salicylates have significant anticoagulant and fibrinolytic activity [88,89].

Anti-inflammatory activity

Traditionally, oral adminstration of meadowsweet was known as a common treatment for inflammatory diseases, attributed to its high content of phenolic compounds [90-92]. Aqueous extract of *F. ulmaria* is rich in ellagitannins which can contribute to the formation of urolithin A, B, and C in oral administration, and these gut microbiota metabolites can significantly inhibit TNF-α production especially urolithin A at nanomolar concentrations [5]. In vitro assessment of meadowsweet has shown that methanol extracts of aerial parts and roots can inhibit the Cox-1 and -2 enzymes function. In fact, the extract of aerial parts has exhibited two times higher inhibitory effects in comparison to roots. The extract has prohibited COX-2 gene expression in the THP-1 cell line. In one study, using hot plate method indicated that a dose of 100 and 200 mg/kg of extract from the root and aerial parts of meadowsweet could increase the latency time. In the carrageenan-induced acute inflammation test, 100 and 200 mg/kg of aerial parts extract and 200 mg/kg of root extract could decrease average rat paw swelling [77]. Oral doses of 100–300 mg/kg from lyophilized flower infusions showed significant dose-dependent anti-hyperalgesic activity but did not affect edema reduction [91]. Aqueous extract of aerial parts could inhibit the production of TNF-α and IL-1β. The main polyphenols of the extract are apigenin, quercetin, salicylic acid which can reduce inflammation by decreasing macrophage numbers in humans [92]. The hydro-alcoholic extract showed potent inhibition of lipoxygenase activity by the IC_{50} of 0.5 mg/mL [93]. Santoro D, exhibited that the extract, in combination with boldo extract, in low concentration may affect the expression of β-defensins (cBD) and cathelicidin (cCath) without showing any pro-inflammatory property in canine keratinocyte [94]. Isolated flavonoids (kaempferol 4′-*O*-*β*-D glucoside, astragalin 2″-*O*-gallate and a mixture of isoquercitrin 2″-*O*-gallate and hyperoside 2″-*O*gallate; spiraeoside) from lyophilized flower infusions were evaluated for their abilities to inhibit prostaglandin E2 (PGE2), thromboxane B2 (TXB2) and 12(S)-hydroxy-(5*Z*,8*Z*,10*E*,14*Z*)-eicosatetraenoic acid (12-HETE) productions.The results showed that the lyophilized flower infusion of *F. ulmaria* have higher inhibitory activity against eicosanoid production (12-HETE and PGE-2 with IC_{50} 3.415 and 6.768 mg/mL, respectively) comparable to control (acetylsalicylic acid and quercetin). Astragalin 2″-*O*-gallate (IC_{50} =141.1 μg/mL) and spiraeoside (IC_{50} =4.69 μg/mL) showed potent activity against PGE2 and 12-HETE in human platelets [95]. The anti-inflammatory effect of methanol extracts of meadowsweet on COX-2/PGE2 (in vitro), promoted function of monocyte and neutrophil against inflammatory factors and stimulated the secretion of the cytokines, especially Th1 lymphocyte (IL-6, IL-1β, and TNF-α) and Th17 lymphocytes (i.e. IL-21 and IL-23) that are associated with pro-inflammatory likely immunostimulant [96]. These observations support the use of extract for relieving pain and inflammatory disease in folk medicines.

Anti-cancer effects

Filipendula ulmaria has been studied in various cancer cell lines, especially breast tumors, where it showed a notable impact in decreasing multiplicity and malignant tumors incidence in female LIO rats that were treated with *F. ulmaria* and drinking water during 16 months [97]. Furthermore, another study examined the incidence and multiplicity of CNS and spinal cord tumors in rats. Pregnant rats of LIO strain were given single i.v. injection of ethyl-nitrosourea (ENU) on the 21st day of gestation. Postnatal decoction of meadowsweet, significantly reduced the incidence and multiplicity of CNS tumors (brain-by 2.0 and 2.1 times, spinal cord-by 3.1 and 3.0 times, respectively, number of tumor-bearing rats (by 1.2 times) and significantly increased latency period [67]. Meadowsweet extract showed a statistically considerable impact in decreasing the incidence and multiplicity of colorectal tumors induced by the methyl-nitrosourea in rats, by 2.0 and 2.8 times, respectively [98]. In another study, inhibition of the proliferation of three cell lines, breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460) and melanoma (A375-C5) were examined by using several extraction methods. Although all the extracts inhibited growth of the studied cell lines, the most potent one was obtained by decoction (GI_{50} values 63.3, 96.0, 70.0 μg/mL for A375-C5, MCF-7 and NCI-H460 cell lines, respectively). Decoction, methanol and methanol:water (80/20) (v/v) extraction on MCF-7 cells presented similar effect of cell growth inhibition (GI_{50}: 96, 91.5,

and 96.3 μg/mL, respectively) [99]. Reports about the influence of *F. ulmaria* extract (5 mg/mL) on murine neuroblastoma malignant tumor cell, showed weak to moderate range of effectiveness (LC_{50} = 2.528-4.939 mg/mL) [100]. The in vitro in 26 mice demonstrated apoptotic and antiproliferative activity of the pollen methanol extracts of *F. ulmaria* and showed high efficiency and apoptotic index (1 mg/mL concentration of extracts) at 24 and 48 h of treatment (~30% of inhibition) [101]. Local administration of a decoction from flowers of *F. ulmaria* in mice reduced the frequency of squamous-cell in vagina and cervix carcinoma by 39%. In addition, the clinical evaluation on the ointment of *F. ulmaria* indicated complete regression of dysplasia in 67% of patients from 48 cases of cervical dysplasia [102]. The EtOH extracts (70%) of meadowsweet, at the dose of 50 and 100 mg/kg, showed dose-dependent anti-metastatic action in C57BL/6 mice with Lewis lung carcinoma (LLC) and reduced the level of metastasis area by 1.5 and 1.7 times, respectively. The combined use of *F. ulmaria* extract at doses of 50 and 100 mg/kg and cyclophosphamide (125 mg/kg) decreased the tumor mass and metastasis area in mice with LLC [103].

Gastro-protective effects

The gastroprotective effect of *F. ulmaria* extract was assessed in the rat model of ethanol-induced gastric lesions. One hour prior to induction of gastric lesions, the rats were treated with intra-gastric administration of *F. ulmaria* extract (100–300 mg/kg). The rats in the positive group received ranitidine (20 mg/kg, p.o.) and rats in the negative control group received vehicle (water, 1 mL/kg, p.o.). One hour after the lesion induction, the animals were sacrificed and the lesions were studied. The average gastric damage scores (GDSs) in rats treated with meadowsweet extracts were in the range of 1.4–2.9 ($p<0.05$) and the lesions in the highest dose (300 mg/kg) were very small, indicating excellent therapeutic efficacy compared to the control groups (GDSs 1.4±2.01). Positive control (ranitidine) clearly protected the tissue and mucus of the stomach (GDS 2.5, $p<0.01$), while the negative control group (received water) showed the most damage to the tissue and mucosa of the stomach (GDS 6). This study demonstrated the gastro-protective effect of meadowsweet extract [95]. Moreover, in traditional medicine, meadowsweet has been used for gastro-protective effects and its ability to treat dyspepsia [104,105].

Hepato-protective effects

Worldwide, liver diseases account for 3.5% of all deaths.. The medicinal resources for the treatment of these diseases are scarce and the duration of treatment is long [106,107]. On the other hand, hepatotoxicity is one of the major side effects of certain drugs and toxins [105, 108]. In cisplatin-induced hepatotoxicity, Wistar rats with increased level of aspartate transaminase (AST) and alanine transaminase (ALT), were treated by 200 and 400 mg/kg of methanol extracts from roots and aerial parts of *F. ulmaria*, that led to the reduction in the oxidative stress markers (superoxide-dismutase and catalase) and also lowered the enzymatic activity of ALT and AST , levels of malonyl dialdehyde (MDA) and glutathione (GSH) [108]. *Filipendula ulmaria* aerial parts extract (with daily dose 100 mg/kg) demonstrated the most potent hepato-protective activity in 112 rats with CCl_4-induced hepatotoxicity. Meadowsweet extracts (ethanol 70 and 95%) improved the weight index in rats with liver toxicity and the levels of lipid peroxidation (LPO) to normal and. The etxract decreased lipid hydroperoxides (LHP) content 2.6 times compared to the CCl_4 control group [94]. Besides, the extract has been effective on hepatocyte injury markers (AST, ALT, LPO) and anti-oxidant defense systems in liver cells [19]. Its mechanism is probably based on the fact that meadowsweet has stabilized the structure of liver cells and their functions [105].

Immunomodulatory properties

Methanol, ethyl acetate, and the aqueous extracts of *F. ulmaria* roots and the methanol extracts of flowers and aerial parts have a strong inhibitory effect on the complement activation in humans and they interfere with reactive oxygen species (ROS) production and T-cell proliferation [109]. These results are based on the luminol-dependent chemiluminescence generated by zymosan-stimulated human neutrophils (PMNs) and T-cell proliferation test. They can be related to the presence of tannins and flavonoids in the plant. [110,111].

Anti-microbial activity

Aqueous leaf extract of meadowsweet exhibited no significant antimicrobial activity against 34

pathogenic bacterial and fungal isolates on Columbia blood agar [112]. Results of another study suggested that *F. ulmaria* showed clear antimicrobial capacity against *Listeria monocytogenes* Scott A using the disk diffusion method [63]. In another study, the hydroethanolic extract of *F. ulmaria* had no significant anti-adhesion activity (IC_{50} values>35 mg/mL) against *Campylobacter jejuni* [113]. The antimicrobial activity of aerial parts was screened against eleven foodborne pathogens by the agar diffusion method. It has shown strong activity (inhibition zone above 20 mm) against *S. aureus* strains, *P. vulgaris, K. pneumoniae,* and *C. albicans* even in a 2% solution. Among these four strains, the lowest MIC_{50} values 0.08 mg/mL were observed against *P. vulgaris* and *K. pneumonia.* Luminometric measurement of the antibacterial effect of the plant extract on *E. coli* viability has shown the highest antibacterial activity (75% inhibition of control) [64]. Meadowsweet showed bactericidal activity against *Staphylococcus aureus* and *Escherichia coli* using the Cylinder diffusion method [114]. Flower extract of *F. ulmaria* revealed antifungal effects against *Candida* species (*C. albicans*, *C. glabrata*, *C. parapsilosis,* and *C. tropicalis*) by CFU counts and MIC_{50} values <0.05 mg/mL on *C. glabrata*, *C. parapsilosis* [79]. Antibiotic activity of extracts from rhizomes, leaves, flowers, and upper stems were examined by anti-biograms and by dilution in the bacterial medium. The antibiotic activity was observed against *Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, Shigella flexneri, Klebsiella pneumoniae,* and *Bacillus subtilis* in concentrations of 5% and 10% (g extract to 100 mL culture medium) [115]. Another study showed that aqueous-methanol extract of *F. ulmaria* demonstarated antibacterial activity due to phenolic contents. Acidic conditions help to intensify this activity especially against *Salmonella enteritidis* and *Listeria monocytogenes* species. Higher concentrations of the extract could inhibit spoilage bacteria. [116,117].

Anti-oxidant activity

Meadowsweet flower extracts showed strong antioxidant activity by the TBARs (thiobarbituric acid reactive substances) in comparison to hawthorn inflorescence [62]. Pulverized plant and methanol extract indicated significant antioxidant activity by the Rancimat method and [63]. Ethanol extracts (70% and 95%) of the above-ground part, showed strong antioxidant activity. [118]. Meadowsweet extracts showed strong activity using ORAC (oxygen radical absorbance capacity), TRAP (total peroxyl-radical antioxidant parameter), HORAC (hydroxyl radical averting capacity), and inhibition of lipid peroxidation methods because it is rich in chain-braking polyphenolic antioxidants [64]. Hydro-alcoholic plant extract had a high activity with DPPH and superoxide radical in comparison to vitamin E and quercetin as reference standards [95,119,120]. Lyophilized flower infusions) of *F. ulmaria* and its isolated flavonoid spiraeoside exhibited pronounced activities in DPPH-radical scavenging and FRAP antioxidant assays [95]. Aqueous and the methanol extracts of *F. ulmaria* were mostly active against hydroxyl and superoxide radicals especially the aqueous extract [121]. The ethanolic extract from *F. ulmaria* collected from Romania also indicated significant antioxidant activity via DPPH assay [122]. In another study, The ethanolic extracts had a higher activity in DPPH and reducing power assay compared to the aqueous one [123]. Total phenolic content (TPC) of the methanol extract by Folin-Ciocalteu assay was 52.4±0.6to 112.6±4.8 mg GAE/g dry weight of extract (DWE) [120]. Aqueous and aqueous-alcoholic extracts exhibited strong bromine-scavenging activity [124]. Considerable content of phenolic compounds in the methanol extracts especially phenolic acids and flavonoids in aerial parts have a clear correlation with the antioxidant capacity. Polyphenol contents as natural antioxidants seem to be effective in oxidative stress-related diseases [11,29].

Toxicity

The complete German commission E monographs lists have not stated any contraindications for *F. ulmaria* adminstration (except in people with salicylate sensitivity) [125]. The US Food and Drug Administration has classified the plant as an herb of undefined safety. The LD_{50} of the ethanol extract of meadowsweet in rabbits is reported to be 1770 mg/kg for intraperitoneal administration and 75.7 mg/ kg for intravenous administration [127]. The LD_{50} of 1:20 meadowsweet decoction used intraperitoneally administered to mice has been 535 mg/kg in males and 1050 mg/kg in females.

The LD_{50} of the decoction in rabbits has reported to be 141.5 mg/kg after intravenous administration [127]. No adverse effects on liver function were observed in rabbits treated with different extracts of meadowsweet (extracts, doses, and duration of treatment not specified in available English translations) [128].

Medicinal information

In some countries, the plant is prepared as capsules for oral use containing 250–300 mg of powdered herbal substance or 169–200 mg of dry aqueous extract (daily dose: 250-1500 mg), as sachets for herbal tea preparation containing 1.5 g of comminuted herbal substance, tinctures dry and ethanol concentration are 100-150 mg and as hard capsules for oral use containing 50 mg of dry ethanolic extract [126]. Also, meadowsweet is used as an herbal ingredient in various pharmaceutical supplements. *F. ulmaria* can be used to synthesize aspirin from salicylic acid and its derivatives [14,47,69,129-131]. However, aspirin in high doses and long-term use can have a devastating effect on the stomach causing stomach ulcers *F. ulmaria* has protective effects on the mucosa of the stomach and intestine due to it's anti-inflammatory activity [4,132,133]. Aspirin is known to develop an acute liver injury in high doses and long term use however *F. ulmaria* has hepatoprotective effects [19,134]. Due to the presence of salicylate compounds in this plant, it can increase the anticoagulation potential of anticoagulant agent so its concomitant use with anticoagulants or antiplatelet drugs, non-steroidal anti-inflammatory drugs (NSAIDs), and all drugs and foods that have anticoagulant effect may increase the risk of bleeding and it should be avoided in patients with anticoagulant therapy [133,135]. Regarding contraindication of *F. ulmaria*, it should not be used by patients with hypersensitivity to salicylates or sulfites [20]. Usage in children and adolescents under 18 years of age is not recommended. Asthma patients should be careful while using this herb because bronchospasm side effect has been reported. Meadowsweet safety during pregnancy and lactation has not been established, so due to insufficient information, uses during pregnancy and lactation is avoided [14, 126].

The outcomes of our review on *F. ulmaria* have revealed that Meadowsweet can be considered as a valuable medicinal plant [4,12,126]. Most important compounds of this plant, are salicylate derivatives with analgesic, anticoagulant, anti-inflammatory, and anti-arthritis effects. According to *in-vitro* and *in-vivo* studies on anti-inflammatory activity, methanol and aqueous extract of *F. ulmaria* roots and aerial parts have shown the inhibition of COX-2 gene expression, TNF-α and IL-1β production due to their polyphenolic contents such as apigenin, quercetin and salicylic acid [77,94]. Additionally, an aqueous and hydro-alcoholic extracts of meadowsweet exhibited a strong anti-oxidant activity by ORAC, TRAP, HORAC, DPPH and an inhibition of lipid peroxidation via polyphenolic compounds, such as phenolic acids and flavonoids mainly found in aerial parts [64]. Diverse biological effects, such as anti-oxidant and cyto-protective properties, may contribute to the plant's safety in the body. In different studies, treatment of rats and cancer cell lines with *F. ulmaria*, demonstrated positive and noteworthy effects on breast tumors and breast adenocarcinoma, on human tumors of the central nervous system (CNS and spinal cord tumors), on colorectal tumors, non-small cell lung cancer, melanoma, and squamous-cell carcinoma of the rat's vagina and cervix [98,99,102]. As a result, *F. ulmaria* might show a high potential for treating malignant cells expressed by main compounds such as kaempferol, quercetin, apigenin, and luteolin [49,136-141]. Also, some triterpene compounds, such as ursolic acid, pomolic acid, and beta-carotene have illustrated anti-tumor and anti-cancer effects [57,59,142,143]. In addition, apigenin is mentioned as an essential compound of the plant in treating of gastrointestinal disorders [50]. Regarding the immunomodulatory effects, the responsible substances can be tannins and flavonoids [144]. Moreover, *F .ulmaria* has demonstrated antimicrobial activity. Antimicrobial effects on foodborne pathogens such as *S. aureus* strains, *P. vulgaris, K. pneumonia*, and *C. albicans* can be due to phenolic compounds [145,146]. Currently, the plant has been used in many herbal supplements, and is indicated for the treatment of the following diseases: rheumatic disorder (osteoarthritis, rheumatism, musculoskeletal, and joint disorder), gastrointestinal disease (dyspepsia, gastric hyperacidity, heartburn, digestive disorder, and flatulence), and as a diuretic (kidney disorder, renal calculi, constipation, urinary-tract disorder). Furthermore, some medicinal supplements recorded in Martindale, considered *F. ulmaria* as

a part of their regimens to control influenza symptoms and as an analgesic (in migraine and headache) [147,148].

Conclusion

Filipendula ulmaria from Rosaceae family, is a perennial, herbaceous plant and is native throughout Europe and Western Asia. Traditionally, this herb was used as a remedy for inflammatory diseases and renal elimination function. It contains various metabolites such as phenolic acids, flavonoids, tannins, and terpenoids. Different investigations on anti-inflammatory, anti-oxidant, anti-microbial, anti-coagulant and anti-cancer activities and its protective effects on liver and stomach have been reviewed in this study. In addition, some medical and toxicity information have also been explained. Further clinical studies are required to assess the traditional uses of the plant and the pharmacokinetic of its active components.

Acknowledgments

None.

Author contributions

Mahdieh Kalkhorani Designed the study; Mahdieh Kalkhorani and Avishan Farzaneh reviewed the pharmacological and phytochemical studies and drafted the manuscript; Azadeh Manayi and Roodabeh Bahramsoltani contributed in conception and revised the manuscript critically. Abbas Hadjiakhoondi and Mahnaz Khanavi, contributed in designing the study and supervised the study.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

References

[1] United States Department of Agriculture. *Filipendula ulmaria*. [Accessed 2021]. Available from http: //plants.usda.gov/ home/ plantProfile? symbol= FIUL.

[2] Prior RC. On the popular names of British plants, being an explanation of the origin and meaning of the names of our indigenous and most commonly cultivated species. 2nd ed. London: Williams and Norgate, 1870.

[3] Van der Kooi CJ, Pen I, Staal M, Stavenga DG, Elzenga JTM. Competition for pollinators and intra-communal spectral dissimilarity of flowers. *Plant Biol.* 2016; 18(1): 56–62.

[4] Hadjiakhoondi A, Baligh N. Practical guide to medicinal plants. 1st ed. Tehran: Scientific Publishing Center, 2002.

[5] Piwowarski JP, Granica S, Zwierzynska M, Stefanska J, Schopohl P, Melzig MF. Role of human gut microbiota metabolism in the anti-inflammatory effect of traditionally used ellagitannin-rich plant materials. *J Ethnopharmacol*. 2014; 155(1): 801–809.

[6] Katanic J, Matic S, Pferschy-Wenzig EM, Kretschmer N, Boroja T, Mihailovic V. *Filipendula ulmaria* extracts attenuate cisplatin-induced liver and kidney oxidative stress in rats: In vivo investigation and LC-MS analysis. *Food Chem Toxicol.* 2017; 99(1): 86–102.

[7] Šarić-Kundalić B, Dobeš C, Klatte-Asselmeyer V, Saukel J. Ethnobotanical survey of traditionally used plants in human therapy of east, north and north-east Bosnia and Herzegovina. *J Ethnopharmacol*. 2011; 133(3): 1051–1076.

[8] McCormack J, Power I. Nonsteroidal anti-inflammatory drugs and acetaminophen: pharmacology for the future. In: Raymond S, Ed. Acute pain management. New York: Cambridge University Press, 2009.

[9] Mitra SP. Pharmacology and biochemistry behind the use of natural herbs to control arthritis, a review. *Indian J Nat Prod Resour*. 2017; 8(3): 204–223.

[10] Katanic J, Boroja T, Stankovic N, Mihailovic V, Mladenovic M, Kreft S. Bioactivity, stability and phenolic characterization of *Filipendula ulmaria* (L.) Maxim. *Food Funct.* 2015; 6(4): 1164–1175.

[11] Voicu SN, Hermenean A, Olah NK, Badulescu L, Stan MS, Dinischiotu A. Designing new mother tinctures for increased antioxidant efficiency on inflammatory intestinal diseases. *Farmacia*. 2019; 67(2): 290–295.

[12] Popowski D, Pawłowska KA, Piwowarski JP, Granica S. Gut microbiota-assisted isolation of flavonoids with a galloyl moiety from flowers of meadowsweet, *Filipendula ulmaria* (L.) Maxim. *Phytochem Lett.* 2019; 30(4): 220–223.

[13] Sile I, Romane E, Reinsone S, Maurina B,

Tirzite D, Dambrova M. Medicinal plants and their uses recorded in the archives of Latvian folklore from the 19th century. *J Ethnopharmacol*. 2020; 249(3): 1–15.

[14] Garcia-Oliveira P, Fraga-Corral M, Pereira A, Lourenço-Lopes C, Jimenez-Lopez C, Prieto M. Scientific basis for the industrialization of traditionally used plants of the Rosaceae family. *Food Chem.* 2020; 330(11): 1–16.

[15] Braun L, Cohen M. Herbs and natural supplements: an evidence-based guide. 4th ed. Melbourne: Elsevier Health Sciences, 2015.

[16] Parnell J, Curtis T, Cullen E. Webb's an Irish Flora. 8th ed. Cork: Cork University Press, 2012.

[17] Clapham AR, Tutin TG, Warburg EF. Excursion flora of the British Isles. 3rd ed. Lincoln: Cambridge University Press, 1981.

[18] Brunke EJ, Hammerschmidt FJ, Schmaus G. Flower scent of some traditional medicinal plants. In: teranishi R, Ed. bioactive volatile compounds from plants. Washington: American Chemical Society, 1993.

[19] Halkes SBA, Beukelman CJ, Kroes BH, Van den Berg AJ, Labadie RP, Van Dijk H. In vitro immunomodulatory activity of *Filipendula ulmaria*. *Phytoter Res.* 1997; 11(7): 518–520.

[20] Jackson B, Wichtl M. Herbal drugs and phytopharmaceuticals: a handbook for practice on a scientific basis. 2nd ed. Stuttgart: Medpharm Scientific Publishers, 1994.

[21] Van Hellemont J. Fytotherapeutisch compendium. 2nd ed. Utrecht: Bohn Scheltema and Holkema, 1988.

[22] Zeylstra H. *Filipendula ulmaria*. *Br J Phytoter*. 1998; 5(3): 8–12.

[23] Mclntyre M. British herbal compendium. A handbook of scientific information on widely used plant drugs. Dorset: British Herbal Medicine Association, 1993.

[24] Bassi P, Kumar V, Kumar S, Kaur S, Gat Y, Majid I. Importance and prior considerations for development and utilization of tea bags: a critical review. *J Food Process Eng*. 2020; 43(1): 1–10.

[25] Bradely P. British herbal pharmacopoeia. Bournemouth: British Herbal Medicine Association, 1990.

[26] House L. British herbal pharmacopoeia. Cowling: British Herbal Medicine association, 1983.

[27] Madaus G. Lehrbuch der biologischen Heilmittel. Leipzig: Georg Thieme Verlag, 1938.

[28] Gessner O, Orzechowski G. Poisonous and medicinal plants from Central Europe. Heidelberg: Carl Winter Universitatverlag, 1974.

[29] Dorsch PM, Swanson SR, Kelley SW. The role of relationship quality in the stratification of vendors as perceived by customers. *J Acad Mark Sci*. 1998; 26(2): 128–142.

[30] Blumenthal M, Busse WR, Goldberg A, Gruenwald J, Hall T, Riggins CW. The complete German commission E monographs: therapeutic guide to herbal medicines. Austin: American Botanical Council, 1998.

[31] Schulz V, Hansel R, Tyler VE. Rational phytotherapy: a physician′s guide to herbal medicine. 3rd ed. Berlin: Springer-Verlag, 1998.

[32] Chrubasik S. The scientific foundation for herbal medicinal products. 2nd ed. New York: Thieme, 2009.

[33] Barnes J, Anderson L, Phillipson D. Herbal medicines. 3rd ed. London: Pharmaceutical Press, 2007.

[34] Rasouli H, Farzaei MH, Khodarahmi R. Polyphenols and their benefits: a review. *Int J Food Prop.* 2017; 20(12): 1700–1741.

[35] Bahramsoltani R, Kalkhorani M, Zaidi SMA, Farzaei MH, Rahimi R. The genus *Tamarix*: traditional uses, phytochemistry, and pharmacology. *J Ethnopharmacol*. 2019; 246(1): 1–24.

[36] Khanavi M, Hajimahmoodi M, Cheraghi-Niroomand M, Kargar Z, Ajani Y, Hadjiakhoondi A. Comparison of the antioxidant activity and total phenolic contents in some *Stachys* species. *Afr J Biotechnol*. 2009; 8(6): 1143–1147.

[37] Baranenko D, Bespalov V, Nadtochii L, Shestopalova I, Chechetkina A, Lepeshkin A. Development of encapsulated extracts on the basis of meadowsweet (*Filipendula ulmaria*) in the composition of functional foods with oncoprotective properties. *Agron Res*. 2019; 17(5): 1829–1838.

[38] Bijttebier S, Peeters L, Foubert K, Hermans N, Pieters L. An integrated strategy to characterize new anti-inflammatory lead compounds derived from *Filipendula*

ulmaria (meadowsweet). *Planta Med.* 2019; 85(18): 240.

[39] Farzaei MH, Khanavi M, Moghaddam G, Dolatshahi F, Rahimi R, Shams-Ardekani MR, Amin G, Hajimahmoodi M. Standardization of *Tragopogon graminifolius* DC. extract based on phenolic compounds and antioxidant activity. *J Chem.* 2014; Article ID 425965.

[40] Jafari S, Moradi A, Salaritabar A, Hadjiakhoondi A, Khanavi M. Determination of total phenolic and flavonoid contents of *Leonurus cardiaca* L. in compare with antioxidant activity. *Res J Biol Sci*. 2010; 5(7): 484–487.

[41] Katanić J, Pferschy-Wenzig EM, Mihailović V, Boroja T, Pan SP, Nikles S. Phytochemical analysis and anti-inflammatory effects of *Filipendula vulgaris* Moench extracts. *Food Chem Toxicol*. 2018; 122(12): 151–162.

[42] Pukalskienė M, Venskutonis P, Pukalskas A. Phytochemical composition and antioxidant properties of *Filipendula vulgaris* as a source of healthy functional ingredients. *J Funct Foods.* 2015; 15(5): 233–242.

[43] Kumar N, Goel N. Phenolic acids: natural versatile molecules with promising therapeutic applications. *Biotechnol Rep*. 2019; 24(12): 1–10.

[44] Olennikov DN, Kruglova MY. A new quercetin glycoside and other phenolic compounds from the genus *Filipendula*. *Chem Nat Compd*. 2013; 49(4): 610–616.

[45] Adamczak A, Ożarowski M, Karpiński TM. Antibacterial activity of some flavonoids and organic acids widely distributed in plants. *J Clin Med.* 2020; 9(1): 1–17.

[46] Sharma A, Sidhu GPS, Araniti F, Bali AS, Shahzad B, Tripathi DK. The role of salicylic acid in plants exposed to heavy metals. *Molecules*. 2020; 25(3): 1–22.

[47] Papp I, Simándi B, Blazics B, Alberti Á, Héthelyi É, Szoke É. Monitoring volatile and non-volatile salicylates in *Filipendula ulmaria* by different chromatographic techniques. *Chromatographia*. 2008; 68: 125–129.

[48] Blazics B, Papp I, Kéry A. LC-MS qualitative analysis and simultaneous determination of six *Filipendula salicylates* with two standards. *Chromatographia*. 2010; 71: 61–67.

[49] Kikuchi H, Yuan B, Hu X, Okazaki M. Chemopreventive and anticancer activity of flavonoids and its possibility for clinical use by combining with conventional chemotherapeutic agents. *Am J Cancer Res*. 2019; 9(8): 1517–1535.

[50] Kalkhorani M, Hadjiakhoondi A, Yassa N, Amin M, Damankash S, Moradkhani F. Bioguided fractionation of *Centaurea bruguierana* subsp. *belangeriana* extract based on anti-*Helicobacter pylori*. *Res J Pharmacogn.* 2020; 7(1): 61–67.

[51] Almasian A, Najafi F, Eftekhari M, Ardekani MRS, Sharifzadeh M, Khanavi M. Polyurethane/ carboxymethylcellulose nano fibers containing *Malva sylvestris* extract for healing diabetic wounds: preparation, characterization, in vitro and in vivo studies. *Mater Sci Eng C Mater Biol Appl.* 2020; 114(9): 1–14.

[52] Rathee P, Chaudhary H, Rathee S, Rathee D, Kumar V, Kohli K. Mechanism of action of flavonoids as anti-inflammatory agents: a review. *Inflamm Allergy Drug Targets*. 2009; 8(3): 229–235.

[53] Uritu CM, Mihai CT, Stanciu GD, Dodi G, Alexa-Stratulat T, Luca A. Medicinal plants of the family Lamiaceae in pain therapy: a review. *Pain Res Manag.* 2018; Article ID 7801543.

[54] Faggio C, Sureda A, Morabito S, Sanches-Silva A, Mocan A, Nabavi SF. Flavonoids and platelet aggregation: a brief review. *Eur J Pharmacol*. 2017; 807(7): 91–101.

[55] Asgarpanah J, Motamed SM, Farzaneh A, Ghanizadeh B, Tomraee S. Antioxidant activity and total phenolic and flavonoid content of *Astragalus squarrosus* Bunge. *Afr J Biotechnol.* 2011; 10(82): 19176–19180.

[56] Goodarzi S, Hadjiakhoondi A, Yassa N, Khanavi M, Tofighi Z. Essential oils chemical composition, antioxidant activities and total phenols of *Astrodaucus persicus*. *Iran J Basic Med Sci.* 2016; 19(2): 159–165.

[57] Wang X, Zhang F, Yang L, Mei Y, Long H, Zhang X. Ursolic acid inhibits proliferation and induces apoptosis of cancer cells in vitro and in vivo. *Biomed Res Int.* 2011; Article ID 419343.

[58] Davis EM, Croteau R. Cyclization enzymes in the biosynthesis of monoterpenes, sesquiterpenes and diterpenes. *Biosynthesis*. 2000; 209(11): 53–95.

[59] Neto CC, Vaisberg AJ, Zhou BN, Kingston

DG, Hammond GB. Cytotoxic triterpene acids from the Peruvian medicinal plant *Polylepis racemosa*. *Planta Med*. 2000; 66(5): 483–484.

[60] Williams AC, Barry BW. Penetration enhancers. *Adv Drug Deliv Rev.* 2012; 64(12): 128–137.

[61] Nitta Y, Kikuzaki H, Azuma T, Ye Y, Sakaue M, Higuchi Y, Komori H, Ueno H. Inhibitory activity of *Filipendula ulmaria* constituents on recombinant human histidine decarboxylase. *Food Chem*. 2013; 138(2-3): 1551–1556.

[62] Sroka Z, Cisowski W, Seredynska M, Luczkiewicz M. Phenolic extracts from meadowsweet and hawthorn flowers have antioxidative properties. *Z Naturforsch*. 2001; 56(9-10): 739–744.

[63] Proestos C, Boziaris IS, Kapsokefalou M, Komaitis M. Natural antioxidant constituents from selected aromatic plants and their antimicrobial activity against selected pathogenic microorganisms. *Food Technol Biotechnol*. 2008; 46(2): 151–156.

[64] Denev P, Kratchanova M, Ciz M, Lojek A, Vasicek O, Blazheva D. Antioxidant, antimicrobial and neutrophil-modulating activities of herb extracts. *Acta Biochim Pol.* 2014; 61(2): 359–367.

[65] Bijttebier S, Voorspoels S, Apers S, Pieters L. A first step in the quest for the active constituents in *Filipendula ulmaria* (meadowsweet): comprehensive secondary metabolite identification by liquid chromatography-quadrupole orbitrap mass spectrometry. *Planta Med*. 2015; 81(16): 1545–1546.

[66] Krasnov EA, Raldugin VA, Shilova IV, Avdeeva EY. Phenolic compounds from *Filipendula ulmaria*. *Chem Nat Compd*. 2006; 42(2): 148–151.

[67] Bespalov VG, Alexandrov VA, Vysochina GI, Kostikova Vcapital AC, Baranenko DA. The inhibiting activity of meadowsweet extract on neurocarcinogenesis induced transplacentally in rats by ethylnitrosourea. *J Neurooncol*. 2017; 131(3): 459–467.

[68] Gniewosz M, Synowiec A, Kraśniewska K, Przybył JL, Baczek K, Weglarz Z. The antimicrobial activity of pullulan film incorporated with meadowsweet flower extracts (*Filipendulae ulmariae* flos) on post-harvest quality of apples. *Food Control*. 2014; 37(1): 351–361.

[69] Olennikov DN, Kashchenko NI, Chirikova NK. Meadowsweet teas as new functional beverages: comparative analysis of nutrients, phytochemicals and biological effects of four *Filipendula* species. *Molecules*. 2016; 22(1): 16–38.

[70] Fecka I. Qualitative and quantitative determination of hydrolysable tannins and other polyphenols in herbal products from meadowsweet and dog rose. *Phytochem Anal*. 2009; 20(3): 177–190.

[71] Papp I, Apati P, Andrasek V, Blazovics A, Balazs A, Kursinszki L. LC-MS analysis of antioxidant plant phenoloids. *Chromatographia*. 2004; 60: 93–100.

[72] Pukalskienė M, Venskutonis PR, Pukalskas A. Phytochemical characterization of *Filipendula ulmaria* by UPLC/Q-TOF-MS and evaluation of antioxidant activity. *Rec Nat Prod.* 2015; 9(3): 451–455.

[73] Pemp E, Reznicek G, Krenn L. Fast quantification of flavonoids in *Filipendulae ulmaria* flos by HPLC/ESI-MS using a nonporous stationary phase. *Chem Nat.* 2007; 62(7): 669–673.

[74] Bukreeva TV, Shukhobodskii BA. Structure of the main flavonoid glycoside from the flowers of *Filipendula ulmaria*. *Chem Nat Compd*. 1987; 23(5): 631–632.

[75] Krasnov EA, Raldugin VA, Avdeeva EY. Filimarin, a new flavanol glycoside from *Filipendula ulmaria* and its antioxidant activity. *Pharm Chem J*. 2009; 43(11): 613–614.

[76] Sofic E, Copra-Janicijevic A, Salihovic M, Tahirovic I, Kroyer G. Screening of medicinal plant extracts for quercetin-3-rutinoside (rutin) in Bosnia and Herzegovina. *Med Plants Int J Phytomed Relat Ind.* 2010; 2(2): 97–102.

[77] Katanic J, Boroja T, Mihailovic V, Nikles S, Pan SP, Rosic G. Corrigendum to: in vitro and in vivo assessment of meadowsweet (*Filipendula ulmaria*) as anti-inflammatory agent. *J Ethnopharmacol*. 2017; 198(2): 608–609.

[78] Toiu A, Vlase L, Oniga I, Benedec D, Tamas M. HPLC analysis of salicylic acid derivatives from natural products. *Farmacia*. 2011; 59(1): 106–112.

[79] Barros L, Alves CT, Duenas M, Silva S, Oliveira R, Carvalho AM. Characterization

of phenolic compounds in wild medicinal flowers from Portugal by HPLC-DAD-ESI/MS and evaluation of antifungal properties. *Ind Crops Prod.* 2013; 44(1): 104–110.

[80] Hamid KH, Azman NA, Md Shaarani S, Zain N, Ahmad N, Sulaiman AZ, Chik SS, Ishak WF, Almajano Pablos MP. *Alchemilla vulgaris* and *Filipendula ulmaria* extracts as potential natural preservatives in beef patties. *Malaysian J Anal Sci M.* 2017; 21(8): 986–995.

[81] Valle MG, Nano GM, Tira S. The essential oil of *Filipendula ulmaria*. *Planta Med.* 1988; 54(2): 181–182.

[82] Farré-Armengol G, Fernández-Martínez M, Filella I, Junker RR, Peñuelas J. Deciphering the biotic and climatic factors that influence floral scents: a systematic review of floral volatile emissions. *Front Plant Sci*. 2020; 11(7): 1–16.

[83] Hamblin L, Laird A, Parkes E, Walker AF. Improved arthritic knee health in a pilot RCT of phytotherapy. *R Soc Health J.* 2008; 128(5): 255–262.

[84] Matic S, Katanic J, Stanic S, Mladenovic M, Stankovic N, Mihailovic V. In vitro and in vivo assessment of the genotoxicity and antigenotoxicity of the *Filipendula hexapetala* and *Filipendula ulmaria* methanol extracts. *J Ethnopharmacol*. 2015; 174(11): 287–292.

[85] Harbourne N, Jacquier JC, O'Riordan D. Optimisation of the aqueous extraction conditions of phenols from meadowsweet (*Filipendula ulmari*a L.) for incorporation into beverages. *Food Chem.* 2009; 116(3): 722–727.

[86] Kudriashov B, Ammosova I, Liapina L, Osipova N, Azieva L, Liapin G, Basanova A. Heparin from the meadowsweet (*Filipendula ulmaria*) and its properties. *Izv Akad Nauk SSSR Biol.* 1991; 6: 939–943.

[87] Liapina L, Koval'chuk G. A comparative study of the action on the hemostatic system of extracts from the flowers and seeds of the meadowsweet (*Filipendula ulmaria* (L.) Maxim.). *Izv Akad Nauk SSSR Biol.* 1993; 1(4): 625–628.

[88] Kudriashov B, Liapina L, Azieva L. The content of a heparin-like anticoagulant in the flowers of the meadowsweet (*Filipendula ulmaria*). *Farmakol Toksikol.* 1990; 53(4): 39–41.

[89] Chrubasik-Hausmann S. Phytomedicines for inflammatory conditions. In: Ramzan I, Ed. Phytotherapies: efficacy, safety, and regulation. New York: John Wiley and Sons Inc, 2015.

[90] Harbourne N, Marete E, Jacquier JC, O'Riordan D. Stability of phytochemicals as sources of anti-inflammatory nutraceuticals in beverages, a review. *Int Food Res J*. 2013; 50(2): 480–486.

[91] Samardzic S, Tomic M, Pecikoza U, Stepanovic-Petrovic R, Maksimovic Z. Antihyperalgesic activity of *Filipendula ulmaria* (L.) Maxim. and *Filipendula vulgaris* Moench in a rat model of inflammation. *J Ethnopharmacol*. 2016; 193(12): 652–656.

[92] Drummond EM, Harbourne N, Marete E, Martyn D, Jacquier JC, O'Riordan D. Inhibition of proinflammatory biomarkers in thp1 macrophages by polyphenols derived from chamomile, meadowsweet and willow bark. *Phytother Res*. 2013; 27(4): 588–594.

[93] Trouillas P, Calliste CA, Allais DP, Simon A, Marfak A, Delage C, Duroux JL. Antioxidant, anti-inflammatory and antiproliferative properties of sixteen water plant extracts used in the Limousin countryside as herbal teas. *Food Chem.* 2003; 80(3): 399–407.

[94] Santoro D, Ahrens K, Vesny R, Navarro C, Gatto H, Marsella R. Evaluation of the in vitro effect of boldo and meadowsweet plant extracts on the expression of antimicrobial peptides and inflammatory markers in canine keratinocytes. *Re Vet Sci.* 2017; 115(12): 255–262.

[95] Samardzic S, Arsenijevic J, Bozic D, Milenkovic M, Tesevic V, Maksimovic Z. Antioxidant, anti-inflammatory and gastroprotective activity of *Filipendula ulmaria* (L.) Maxim. and *Filipendula vulgaris* Moench. *J Ethnopharmacol*. 2018; 213(3): 132–137.

[96] Cholet J, Decombat C, Vareille-Delarbre M, Gainche M, Berry A, Ogéron C. Comparison of the anti-inflammatory and immunomodulatory mechanisms of two medicinal herbs: meadowsweet (*Filipendula ulmaria*) and harpagophytum (*Harpagophytum procumbens*). *Int J Plant Anim Environ Sci*. 2019; 9(3): 145–163.

[97] Bespalov VG, Baranenko DA, Aleksandrov VA, Semenov AL, Kovan'ko EG, Ivanov SD. Chemoprevention of radiation-induced carcinogenesis using decoction of meadowsweet (*Filipendula ulmaria*) flowers. *Pharm Chem J*. 2019; 52(10): 860–862.

[98] Bespalov VG, Alexandrov VA, Semenov AL, Vysochina GI, Kostikova VA, Baranenko DA. The inhibitory effect of *Filipendula ulmari*a (L.) Maxim. on colorectal carcinogenesis induced in rats by methylnitroso urea. *J Ethnopharmacol*. 2018; 227(12): 1–7.

[99] Lima MJ, Sousa D, Lima RT, Carvalho AM, Ferreira ICFR, Vasconcelos MH. Flower extracts of *Filipendula ulmaria* (L.) Maxim. inhibit the proliferation of the NCI-H460 tumour cell line. *Ind Crops Prod*. 2014; 59(8): 149–153.

[100] Mazzio EA, Soliman KF. In vitro screening for the tumoricidal properties of international medicinal herbs. *Phytother Res*. 2009; 23(3): 385–398.

[101] Mărgăoan R, Zăhan M, Mărghitaş LA, Dezmirean DS, Erler S, Bobiş O. Antiproliferative activity and apoptotic effects of *Filipendula ulmaria* pollen against C26 mice colon tumour cells. *J Apic Sci*. 2016; 60(1): 135–144.

[102] Peresun'ko AP, Bespalov VG, Limarenko AI, Aleksandrov VA. Clinico-experimental study of using plant preparations from the flowers of *Filipendula ulmaria* (L.) Maxim. for the treatment of precancerous changes and prevention of uterine cervical cancer. *Vopr Onkol*. 1993; 39(7-12): 291–295.

[103] Amosova E, Shilova I, Zueva E, Rybalkina OY. Influence of *Filipendula ulmaria* (L.) Maxim. extract on Lewis lung carcinoma development and cytostatic therapy effectiveness in mice. *Pharm Chem J*. 2019; 53(5): 458–461.

[104] Franco JVA, Arancibia M, Szeinman DJ, Alonso IT, Vietto V. Herbal (non-Chinese) medicines for functional dyspepsia. *Cochrane Database Syst Rev*. 2019; 4: 1–16.

[105] Shilova IV, Zhavoronok TV, Suslov NI, Krasnov EA, Novozheeva TP, Veremeev AV. Hepatoprotective and antioxidant activity of meadowsweet extract during experimental toxic hepatitis. *Bull Exp Biol Med*. 2006; 142(2): 216–218.

[106] Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. *J Hepatol*. 2019; 70(1): 151–171.

[107] Akbarzadeh T, Sabourian R, Saeedi M, Rezaeizadeh H, Khanavi M, Ardekani MRS. Liver tonics: review of plants used in Iranian traditional medicine. *Asian Pac J Trop Biomed*. 2015; 5(3): 170–181.

[108] Katanic J, Pferschy-Wenzig EM, Bauer R, Mihailovic V. Meadowsweet (*Filipendula ulmaria*): LC-MS phenolic characterization and ameliorating effect on cisplatin-induced hepatotoxicity. *Planta Med*. 2015; 81(16): 9.

[109] Shilova IV, Zhavoronok TV, Souslov NI, Novozheeva TP, Mustafin RN, Losseva AM. Hepatoprotective properties of fractions from meadowsweet extract during experimental toxic hepatitis. *Bull Exp Biol Med*. 2008; 146(1): 49–51.

[110] Hansen MB, Nielsen SE, Berg K. Re-examination and further development of a precise and rapid dye method for measuring cell growth/cell kill. *J Immunol Methods*. 1989; 119(2): 203–210.

[111] Kroes B, Van Ufford HQ, Boer RT, Van den Berg A, Beukelman C, Labadie R. Modulatory effects of *Artemisia annua* extracts on human complement, neutrophil oxidative burst and proliferation of T lymphocytes. *Phytother Res*. 1995; 9(8): 551–554.

[112] Woods-Panzaru S, Nelson D, McCollum G, Ballard LM, Millar BC, Maeda Y. An examination of antibacterial and antifungal properties of constituents described in traditional Ulster cures and remedies. *Ulster Med J*. 2009; 78(1): 13–15.

[113] Bensch K, Tiralongo J, Schmidt K, Matthias A, Bone KM, Lehmann R. Investigations into the antiadhesive activity of herbal extracts against *Campylobacter jejuni*. *Phytother Res*. 2011; 25(8): 1125–1132.

[114] Rauha JP, Remes S, Heinonen M, Hopia A, Kahkonen M, Kujala T. Antimicrobial effects of Finnish plant extracts containing flavonoids and other phenolic compounds. *Int J Food Microbiol*. 2000; 56(S1): 3–12.

[115] Csedo K, Monea M, Sabau M, Esianu S. The antibiotic activity of *Filipendula ulmaria*. *Planta Med*. 1993; 59(S1): 675.

[116] Boziaris IS, Proestos C, Kapsokefalou M, Komaitis M. Antimicrobial effect of *Filipendula ulmaria* plant extract against

selected foodborne pathogenic and spoilage bacteria in laboratory media, fish flesh and fish roe product. *Food Technol Biotechnol.* 2011; 49(2): 263–270.

[117] Boziaris IS, Proestos C, Kapsokefalou M, Komaitis M. Acid-induced injury renders *Salmonella enteritidis* PT4 sensitive to the antimicrobial action of *Filipendula ulmaria* plant extract. *Int J Food Sci Technol.* 2012; 47(8): 1784–1787.

[118] Shilova IV, Krasnov EA, Korotkova EI, Nagaev MG, Lukina AN. Antioxidant properties of extracts from the above-ground parts of *Filipendula ulmaria*. *Pharm Chem J.* 2006; 40(12): 660–662.

[119] Nikolova M, Dzhurmanski A. Evaluation of free radical scavenging capacity of extracts from cultivated plants. *Biotechnol Equip.* 2009; 23(1): 109–111.

[120] Pukalskiene M, Slapsyte G, Dedonyte V, Lazutka JR, Mierauskiene J, Venskutonis PR. Genotoxicity and antioxidant activity of five *Agrimonia* and *Filipendula* species plant extracts evaluated by comet and micronucleus assays in human lymphocytes and Ames *Salmonella*/microsome test. *Food Chem Toxicol.* 2018; 113(3): 303–313.

[121] Calliste CA, Trouillas P, Allais DP, Simon A, Duroux JL. Free radical scavenging activities measured by electron spin resonance spectroscopy and B16 cell antiproliferative behaviors of seven plants. *J Agric Food Chem.* 2001; 49(7): 3321–3327.

[122] Ciobotaru LGG, Pavel AZ, Poenaru R, Moaca EA, Florescu R, Danciu R. Assessment of the antioxidant effect of ethanolic extracts obtained from *Agrimonia eupatoria* L., *Filipendula ulmaria* (L.) Maxim. and *Filipendula vulgaris* moench collected from the estern part of Romania. *Rev Chim.* 2018; 69(9): 2385–2390.

[123] Neagu E, Paun G, Albu C, Radu GL. Assessment of acetylcholinesterase and tyrosinase inhibitory and antioxidant activity of *Alchemilla vulgaris* and *Filipendula ulmaria* extracts. *J Taiwan Inst Chem Eng*. 2015; 52(7): 1–6.

[124] Abdullin IF, Turova EN, Gaisina GK, Budnikov GK. Use of electrogenerated bromine for estimating the total antioxidant capacity of plant raw materials and plant-based medicinal preparations. *J Anal Chem.* 2002; 57(6): 557–560.

[125] Khanavi M, Hadjiakhoondi A. Comparison of antioxidant activity and total phenol contents of some date seed varieties from Iran. *Iran J Pharm Res*. 2010; 9(2): 141–146.

[126] DerMarderosian A, Liberti L Beutler JA, Grauds C, Tatro DS, Cirigliano M, DeSilva, D. Meadowsweet. Review of natural products. Facts and comparisons. St. Louis: Wolters Kluwer Health Inc, 2012.

[127] Bechtel D, Beyer L, Gurley BJ. Botanical safety handbook. 2nd ed. Boca Raton: Taylor and Francis, 2013.

[128] Barnaulov OD, Boldina IG, Galushko VV, Karatygina GK, Kumkov AV, Lumarenko A, Marminson TG, Shukhobodskii BA. Pharmacological properties of galenical preparations from the flowers of *Filipendula ulmaria* (L.) Maxim. *Rastit Resur*. 1979; 15(S): 399–407.

[129] Klessig DF, Tian M, Choi HW. Multiple targets of salicylic acid and its derivatives in plants and animals. *Front Immunol*. 2016; 7(5): 1–10.

[130] Rezabakhsh A, Mahmoodpoor A, Soleimanpour H. Historical perspective of aspirin: a journey from discovery to clinical practice ancient and modern history. *J Cardiovasc Thorac Res.* 2021; 13(2): 179–180.

[131] Kulyar MF, Bhutta ZA, Ali M, Nawaz S, Asif M. Conventional medicine in the treatment of different diseases as a complementary and alternative medicine. *Turkish J Agric Food Sci Technol*. 2020; 8(6): 1283–1285.

[132] *Filipendula ulmaria*. [Accessed 2020]. Available from: https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/filipendula-ulmaria Chevallier.

[133] Li Z, Wang Z, Shen B, Chen C, Ding X, Song H. Effects of aspirin on the gastrointestinal tract: pros vs. cons. *Oncol Lett.* 2020; 20(3): 2567–2578.

[134] Laster J, Satoskar R. Aspirin-induced acute liver injury. *ACG Case Rep J*. 2014; 2(1): 48–49.

[135] Akram M, Rashid A. Anti-coagulant activity of plants: mini review. *J Thromb Thrombolys*. 2017; 44(3): 406–411.

[136] Yang L, Li H, Yang M, Zhang W, Li M, Xu Y, Li J, Kang J, Zhang J, Guo S. Exploration in the mechanism of kaempferol

for the treatment of gastric cancer based on network pharmacology. *Biomed Res Int*. 2020; Article ID 5891016.
[137] Da J, Xu M, Wang Y, Li W, Lu M, Wang Z. Kaempferol promotes apoptosis while inhibiting cell proliferation via androgen-dependent pathway and suppressing vasculogenic mimicry and invasion in prostate cancer. *Anal Cell Pathol*. 2019; Article ID 1907698.
[138] Bian S, Wan H, Liao X, Wang W. Inhibitory effects of apigenin on tumor carcinogenesis by altering the gut microbiota. *Mediators Inflamm*. 2020; Article ID 7141970.
[139] Wang J, Li T, Zang L, Pan X, Wang S, Wu Y, Wang G. Apigenin inhibits human SW620 cell growth by targeting polyamine catabolism. *Evid based Complement Altern Med.* 2017; Article ID 3684581.
[140] Liao Y, Xu Y, Cao M, Huan Y, Zhu L, Jiang Y, Shen W, Zhu G. Luteolin induces apoptosis and autophagy in mouse macrophage ANA-1 cells via the Bcl-2 pathway. *J Immunol Res*. 2018; Article ID 4623919.
[141] Mutlu Altundağ E, Kasacı T, Yılmaz AM, Karademir B, Koçtürk S, Taga Y, Yalçın AS. Quercetin-induced cell death in human papillary thyroid cancer (B-CPAP) cells. *J Thyroid Res.* 2016; Article ID 9843675.
[142] Rowles JL, Erdman Jr. JW. Carotenoids and their role in cancer prevention. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2020; 1865(11): 1–27.
[143] Martins CDA, Rocha GDG, Gattass CR, Takiya CM. Pomolic acid exhibits anticancer potential against a docetaxel-resistant PC3 prostate cell line. *Oncol Rep*. 2019; 42(1): 328–338.
[144] Brindha P. Role of phytochemicals as immunomodulatory agents: a review. *Int J Green Pharm*. 2016; 10(1): 1–18.
[145] Tofighi Z, Eshaghi A, Asl MM, Tajic AR, Navai MS, Tavakoli S. Investigation of chemical keys for relationship between plants and their unifloral honeys by hydrodistillation and SPME and biological activities of honeys. *Eur Food Res*. 2014; 238(4): 665–673.
[146] Cushnie TT, Lamb AJ. Antimicrobial activity of flavonoids. *Int J Antimicrob*. 2005; 26(5): 343–356.
[147] Petrakou K, Iatrou G, Lamari FN. Ethnopharmacological survey of medicinal plants traded in herbal markets in the Peloponnisos, Greece. *J Herb Med.* 2020; 19(2): 1–79.
[148] Bayer G. Martindale: the complete drug reference. 38th ed. London: Pharmaceutical Press, 2014.

Abbreviations

ALT: alanine transaminase; ALP: alkaline phosphatase; AST: aspartate transaminase, Aq: aqueous; CCl_4: carbon tetrachloride; CNS: central nervous system; COX: cyclooxygenase; DPPH: 2, 2-diphenyl-1-picryl-hydrazyl, EtOH: ethanol; EtAc: ethyl acetate; ENU: N-ethyl-N-nitrosourea; FRAP: ferric reducing ability of plasma; GDS: gastric damage scores; HORAC: hydroxyl radical averting capacity; LC_{50}: lethal concentration 50%; IL: interleukin; LPO: lipid peroxidation; MeOH: methanol; NSAIDs: non-steroidal anti-inflammatory drugs; PGE2: prostaglandin E2; ORAC: oxygen radical absorbance capacity; PMNs: polymorphonuclear; ROS: reactive oxygen species; TBARs: thiobarbituric acid reactive substances; TRAP: total radical-trapping antioxidant parameter; TNF: tumor necrosis factor